

**PI(s) of MSM U01: William Cannon**

**Institution(s): Pacific Northwest National Laboratory**

**MSM U01 Grant Number: U01EB022546**

**Title of Grant: Multi-scale Modeling of Circadian Rhythms: From Metabolism to Regulation and Back**

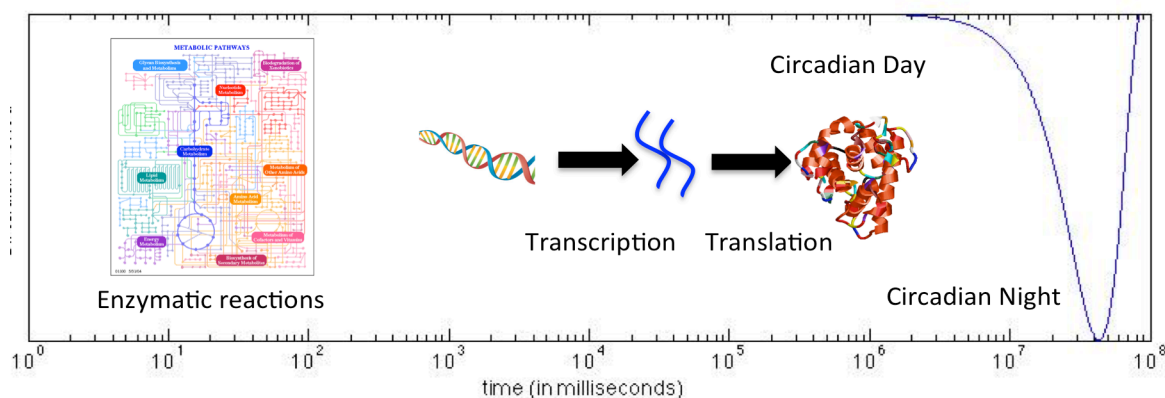
**Abstract Authors**

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**Abstract Text**

**Project Goals:** The goal of this research is to develop and implement a new computational and theoretical method for modeling biological systems that fills a gap in modeling mass action dynamics. Based on statistical thermodynamics, the method bridges data-poor scales (parameters for mass action kinetics) and data-rich scales (chemical potentials of metabolites, and metabolite, protein & transcript data) to enable predictive modeling from enzymatic reactions ( $10^{-3}$  to  $10^0$  s $^{-1}$ ) to gene and protein regulation (~20 minutes) to circadian rhythms (24 hours).

To accomplish this, we are:



Timescales that the simulations using statistical thermodynamics will cover. Enzymatic reactions occur on the millisecond to second timescale while gene and protein expression occur on the minute to ~30 minute scale and the circadian rhythm occurs over a period of 24 hours.

- Implementing an approach to the law of mass action that uses chemical potentials rather than rate constants. This approach involves a rescaling of the fast degrees of freedom, resulting in a compression of the time-dependence to fewer relative scales. Steady state processes can be ‘telescopically’ modeled to address the scale of interest while collapsing faster scales.
- Using the new method to understand the relationship between central metabolism and circadian rhythms in *Neurospora crassa* by using a multi-scale model of metabolism that will include regulation of the circadian clock.

Importantly, environmental controls are known to extensively modulate cellular metabolism in fungi and lead to pre-translational regulation as well [2]. *Neurospora* is commonly used in the study of metabolic regulation and it is also the principal fungal model system for the study of the effects of light and circadian clocks. Our work has found that the clock extensively regulates metabolism via protein expression and may, in turn, be regulated by metabolism itself. Our initial assessment of the expression of central metabolism enzymes suggests that glycolysis and the TCA cycle, generating ATP and NADH, are most active during the circadian dusk, while the pentose phosphate pathway, generating NADPH, is most active during the circadian dawn (left, protein expression indicated by heatmaps). Yet to be determined is whether metabolism oscillates independently between glycolysis and the pentose phosphate pathways, or whether metabolism is controlled by regulation of expression at the protein level [3].

1. Cannon, W.R. and S.E. Baker, *Non-steady state mass action dynamics without rate constants: dynamics of coupled reactions using chemical potentials*. Phys Biol, 2017. **14**(5): p. 055003.
2. Hurley, J.M., et al., *Analysis of clock-regulated genes in Neurospora reveals widespread posttranscriptional control of metabolic potential*. Proc Natl Acad Sci U S A, 2014. **111**(48): p. 16995-7002.

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3. Hurley, J.M., J.J. Loros, and J.C. Dunlap, *The circadian system as an organizer of metabolism*. Fungal Genet Biol, 2016. **90**: p. 39-43.

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